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Serum concentrations of brain-derived neurotrophic factor in patients with gender identity disorder

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ABSTRACT

Gender Identity Disorder (GID) is characterized by a strong and persistent cross-gender identification that affects different aspects of behavior. Brain-derived neurotrophic factor (BDNF) plays a critical role in neurodevelopment and neuroplasticity. Altered BDNF-signaling is thought to contribute to the pathogenesis of psychiatric disordersand is related to traumatic life events. To examine serum BDNF levels, we compared one group of DSM-IV GID patients ($n = 45$) and one healthy control group ($n = 66$). Serum BDNF levels were significantly decreased in GID patients ($p = 0.013$). This data support the hypothesis that the reduction found in serum BDNF levels in GID patients may be related to the psychological abuse that transsexuals are exposed during their life.

1. Introduction

Gender Identity Disorder (GID) is characterized by a strong and persistent cross-gender identification that affects different aspects of behavior(WHO, 1992; APA, 2000). The individuals experience gender dysphoria and desire to live and be accepted as a member of the opposite sex (Dhejne et al., 2011). It is a highly disabling disorder, characterized by intense psychological suffering (Lobato et al., 2006). The recommended treatment may be provided by a multidisciplinary team with physical and psychological assistance, hormone therapy and sex reassignment surgery (Lobato et al., 2006; Salvador et al., 2012). GID is a rare condition, with an estimated worldwide lifetime prevalence ranging 0.001–0.002% (Hoshiai et al., 2010).

The pathophysiology and etiopathogenesis of GID have not been fully elucidated (Selvaggi and Bellringer, 2011). Most of the current hypotheses on the possible cause of transsexuality presume a combination of a genetic background and an early organizational effect on the interaction of sex hormones with the developing brain during critical fetal periods (Garcia-Falgueras and Swaab, 2008). Results from a Dutch research group have showed a neurological basis for gender identity with sexual morphological differentiation of the brain (Garcia-Falgueras and Swaab, 2008; Kruijver et al., 2000; Selvaggi and Bellringer, 2011; Swaab et al., 2002; Zhou et al., 1995).

Lifetime psychiatric comorbidity in GID patients is high, and this should be taken into account in their assessment and treatment planning (Hoshiai et al., 2010). For most GID patients, a strong and persistent identification with the opposite sex and discomfort with one's own sex is a life challenge that often creates distress and carries potential stigmatization (Hoshiai et al., 2010; Matsumoto et al., 2009). Moreover, it was reported that children with GID are at high risk for developing psychiatric problems (Wallien, 2007). Kersting et al. (2003) found a high prevalence of childhood trauma, especially emotional abuse and emotional neglect, in the transsexual sample (Kersting et al., 2003).

Brain-derived neurotrophic factor (BDNF) is a member of the growth factor family, involved in synaptic plasticity, neurogenesis, neuronal survival and normal maturation of neuronal developmental pathways (Fernandes et al., 2009; Gama et al., 2007; Grande et al., 2010) BDNF has a widely reported relation with corticosteroids that appear to play a key role in the environmentally

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mediated vulnerability to psychopathology (Grande et al., 2010). Besides, BDNF serum levels have been associated with traumatic life events and psychiatric disorders (Boulle et al., 2012; Kauer-Sant'Anna et al., 2007).

Given the evidence that GID patients suffer from chronic stress (Kersting et al., 2003; Matsumoto et al., 2009) and that chronic stress and psychiatric disorders are related to a decrease on BDNF levels (Kauer-Sant'Anna et al., 2007), we compared serum BDNF levels in a group of GID patients and a group of healthy controls. The aim of the present study, therefore, was to evaluate whether GID patients have lower BDNF levels than controls.

2. Methods

This study protocol was approved by the Ethical Committee of the Hospital de Clínicas de Porto Alegre, Brazil (HCPA). All subjects were advised about the procedure and signed the informed consent prior to participate in the study. Forty-five GID outpatients from the HCPA Programa de Transtorno de Identidade de Gênero (PROTIG) and sixty-six healthy controls were enrolled in this study protocol. The group of patients had to fulfill Diagnostic and Statistical Manual of Mental Disorders, fourth Edition (DSM-IV) criteria for GID. All patients were under hormone-therapy, using the standard treatment for GID patients. Exclusion criteria were the presence of any comorbid disorder (Axis I and/or Axis II) psychiatric disorder assessed by The Mini International Neuropsychiatric Interview 6.0 (MINI 6.0) (Sheehan et al., 1998) by a trained psychologist. HIV infection, physical intersex conditions, addiction to psychoactive substances, and age below 18 years old were also excluded. Any GID patients currently taking psychotropic medications were also excluded. The control group consisted of medication-free healthy volunteers who had no current, past history or first-degree family history of a major psychiatric disorder, dementia or mental retardation. Subjects and controls were matched for age and belonged to masculine sex.

Five milliliters of blood were withdrawn from each subject by venipuncture into a free-anticoagulant vacuum tube. The samples were centrifuged at 2000*g* during 10 min and serum was kept frozen at −80 °C until assayed. BDNF serum levels were measured with sandwich-ELISA, using a commercial kit according to the manufacturer's instructions (Milipore, USA). Briefly, microtiter plates (96-well flat-bottom) were coated for 24 h at 4 °C with the samples diluted 1:75 in sample diluents and standard curve ranged from 7.8 to 500 pg/ml of BDNF. Plates were then washed four times with wash buffer, added biotinylated mouse anti-human BNDF monoclonal antibody (diluted 1:1000 with sample diluents), and incubated for 3 h at room temperature. After washing, a second incubation with streptavidin–horseradish peroxidase conjugate solution (diluted 1:1000) for 1 h at room temperature was carried out. After addition of substrate and stop solution, the amount of BDNF was determined (absorbance set in 450 nm). The standard curve demonstrates a direct relationship between optical density (OD) and BDNF concentration.

Analysis was performed using Statistical Product and Service Solutions 18.0 Version (SPSS). Mann–Whitney test was used to compare ages. Independent sample *t*-test was conducted to compare BDNF measures. Data were presented as mean ± Standard Deviation (S.D.), and *p*-values <0.05 were considered significant.

3. Results

Demographic characteristics were listed in Table 1. Serum BDNF levels were significantly lower ($p = 0.013$) in GID patients (mean ± S.D.: 17.78 ng/mL ± 5.68) when compared to controls (20.77 ng/mL ± 6.41; Fig. 1). The findings were not interfered by years of education.

Table 1
Characteristics of healthy controls and individuals with GID.

	Individuals with GID ($n = 45$)	Controls ($n = 66$)
Gender (male/female)	100% Male-to-female	100% Male
Age[a]	31.55 (7.7)	30.92 (9.28)
Years of education[a]	10.20 (3.08)	11.42 (3.35)
BDNF[a,b]	17.77 (5.68)	20.76 (6.40)

[a] Mean (S.D.).
[b] $p = 0.013$.

4. Discussion

As far as we know, this is the first study to examine BDNF levels in GID patients. The findings of this study support our hypothesis that BDNF levels are decreased in GID patients comparing to controls.

According to previous studies, lower levels of BDNF were reported in many psychiatric disorders (Begliuomini et al., 2007). Moreover, decreased serum BDNF levels were associated with childhood traumatic events in patients with bipolar disorder (Kauer-Sant'Anna et al., 2007). Kapczinsky et al. (2008) reported that factors that negatively influence the course of BD, such as life stress and trauma have been shown to be associated with a decrease in BDNF serum levels.

Early life events may have long-term effects on adult health and well being, in the form of repeated activation of stress responsive to biological mediators such as glucocorticoids and catechol amines (McEwen, 1998; McEwen and Stellar, 1993). Preclinical studies found that BDNF expression is regulated by stress responsive corticosteroids (Smith et al., 1995). A recent pre-clinical study found that exposure to adverse events early in life might increase the susceptibility to the adverse effects during adulthood (de Lima et al., 2011).

Few clinical studies have investigated the impact of traumatic childhood experiences on sexual identity and GID. Recent studies reported that children with GID are at high risk for developing psychiatric problems in childhood and that the lifetime psychiatric comorbidity in GID patients is high (Matsumoto et al., 2009; Wallien, 2007). Kersting et al. (2003) found a high prevalence of childhood trauma, especially emotional abuse and emotional neglect, in the transsexual sample (Kersting et al., 2003). GID patients are a group affected by stigma and discrimination (Infante et al., 2009; Meyer, 1995, 2003). Stigma, prejudice, and discrimination create a hostile and stressful social environment that causes mental health problems (Meyer, 2003).The concept of social stress

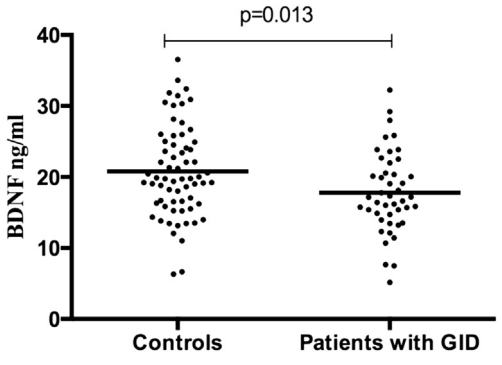

Fig. 1. Levels of serum BDNF in patients with GID and healthy controls.

extends stress theory by suggesting that conditions in the social environment, not only personal events, are sources of stress that may lead to mental and physical ill effects (Meyer, 2003).

Taken together, the reduction found in serum BDNF levels in GID patients could be related to the psychological abuse that they are exposed during their life. As corroborated by Infante et al. (2009), GID is a life challenge that often creates distress and carries potential stigmatization. Overall, these clinical observations are consistent with differences reported in brain structure, metabolic and biochemical changes observed, suggesting a neurological basis for gender identity (Garcia-Falgueras and Swab, 2008; Infante et al., 2009; Kruijver et al., 2000; Selvaggi and Bellringer, 2011; Swaab et al., 2002; Zhou et al., 1995).

Our report must be interpreted in light of its limitations. First, it must be acknowledged that BDNF is complex and influenced by a number of factors (Kauer-Sant'Anna et al., 2007), even thought we have excluded GID patients with Depression diagnosis, we have not applied a scale to identify sub-syndromic depressive symptoms in this group. Second, all of our patients were using hormonal therapy and it is not clear whether it affects our results or not. However, there are some evidence that hormonal replacement therapy with estrogen and progesterone is positively correlated to BDNF in women (Begliuomini et al., 2007; Cubeddu et al., 2011). Third, the lack of female subjects is an important limitation of the study, and our findings are only informative about BDNF levels in male-to-female individuals with GID compared to male controls.

In conclusion, our findings suggest that BDNF levels are decreased in GID patients comparing to controls, an important information about biological markers and gender disorders. Nevertheless, this study gives compelling evidence for larger clinical studies to elucidate the role of BDNF and trauma in GID. Finally, prospective studies of biomarkers in this group of patients, together with neuroimaging techniques, may be informative to elucidate underlying mechanisms of GID.

Conflicts of interest

The authors have declared no conflict of interest in this matter.

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These agencies had no role in the study design, in the acquisition or interpretation of the data, or in writing the report.

Contributors

AMVF designed the study, wrote the protocol, was responsible for the analysis and interpretation of data, participated in data interpretation, drafting the article and final approval of this version. TA, ABC, JS, WJK, BA, PF, ES, MKS and PSBA participated in study design and final approval of this version. MIL, RM, MP, CSG, and FK were responsible for study design and interpretation of data, drafting the article and final approval of this version.

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